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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/930,503	08/16/2001	James L. Henry	39245-173913	1568

7590 07/03/2006

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,503	HENRY ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-137* is/are pending in the application.

4a) Of the above claim(s) *22-33,43,57-68,91-104,107,108 and 126-137* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,34-42,44-56,69-90,105,106 and 109-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Note: this application has been assigned to a different examiner.

Election/Restrictions

Applicant's election without traverse of group I, claims 1-21, 34-42, 44-56, 69-90, 105, 106 and 109-125, directed to methods of treating a pathological condition by administration of a sense or antisense oligonucleotide or oligonucleotide analog in the reply filed on January 19, 2005 and the further election of SEQ ID NO: 41 in the reply filed on March 9, 2006 is acknowledged.

Claims 22-33, 43, 57-68, 91-104, 107, 108 and 126-137 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on January 19, 2005 and March 9, 2006.

Claim Objections

Claims 6, 8, 35, 40, 41, 75 and 76 are objected to because of the following informalities: each of these claims contains non-elected subject matter. Appropriate correction is required.

Claims 18, 45, 79 and 116 are objected to because of the following informalities: in each of these claims the word "subcutaneous" appears twice. Appropriate correction is required.

Applicant is advised that should claims 46, 80 or 117 be found allowable, claims 48, 82 and 119 will be objected to under 37 CFR 1.75 as being substantial duplicates

thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21, 69-90, 105, 106 and 109-125 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 69 and 105 each recite treatment of a condition that is "characterized at least partially" by involvement or activation of the NK-1 receptor. The metes and bounds of these claims cannot be determined because it is unknown if the phrase "at least partially" refers to the involvement of the receptor or if the phrase is meant to refer to characterization of the condition. Claims 2-21, 70-90, 106 and 109-125 are indefinite for the same reasons due to their dependency from one of claims 1, 69 or 105.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21, 34-42, 44-56, 69-90, 105, 106 and 109-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to methods of treating pathological conditions characterized at least partially by involvement of the NK-1 receptor by administration of a compound that interferes with the function or production of NK-1 receptors. In specific embodiments the compound is an oligonucleotide such as an antisense or sense oligonucleotide or a ribozyme. In some embodiments the interference involves at least one nucleic acid in the NK-1 receptor pathway. The pathological conditions include dermatological, immune or autoimmune, cardiovascular, vascular, neuropathic or airway disorders.

The claims encompass the use of a large genus of compounds that interfere with the production or function of the NK-1 receptor. Such compounds include nucleic acid inhibitors such as antisense oligonucleotides or ribozymes as well as non-nucleic acid inhibitors such as antibodies, peptides or small molecules. The genus of compounds usable in the instant methods includes not only those that interfere with the NK-1 receptor itself, but also those that interfere with any nucleic acid within the NK-1 receptor pathway, which includes the nucleic acids that encode transcription factors, ribosomal proteins or any other components of the cellular machinery.

The specification describes use of antisense oligonucleotides to the NK-1 receptor to reduce pain in rats that were exposed to a painful mechanical or chemical stimulus. The specification does not describe the structure of any other compounds encompassed by the claims that inhibit the NK-1 receptor. The antisense oligonucleotides disclosed in the specification and those compounds known in the prior art as antagonists of the NK-1 receptor do not provide a representative sample of the compounds directed to other nucleic acids within the NK-1 receptor pathway such as the numerous components of the cellular machinery involved in production of the NK-1 receptor.

The instant claims are directed to use of compounds that interfere with the NK-1 receptor in order to treat a genus of pathological conditions that involve the NK-1 receptor. Pathological conditions characterized by involvement of the NK-1 receptor are disclosed in the specification as including dermatological disorders, immune disorders, autoimmune disorders, cardiovascular disorders, neuropathic disorders, vascular disorders, gut inflammation, arthritis, airway disorders, psychiatric disorders, central nervous system disorders as well as pain and inflammation of any etiology so long as involvement of the NK-1 receptor is present.

The specification describes the use of antisense oligonucleotides to the NK-1 receptor to reduce pain in rats exposed to a painful stimulus. The description of a method of reducing pain does not provide description of methods for treating the numerous disorders recited in the specification. Using the generic term "immune disorders" as an example, the specification contemplates that the disclosed method will be useful in treating immune disorders, but does not describe what immune disorders

are characterized by involvement of the NK-1 receptor and can be treated by the instantly claimed method. The prior art teaches that the NK-1 receptor is widely expressed in the nervous, cardiovascular and respiratory systems and the gastrointestinal tract and is implicated in pain transmission, vasodilation and smooth muscle contraction. The prior art also teaches that antagonists of the NK-1 receptor have some efficacy in treating conditions such as asthma, migraine and inflammatory skin diseases. The prior art does not provide a description of what immune disorders can be treated by modulation of the NK-1 receptor pathway. Without such a disclosure, the skilled artisan would not be able to recognize whether a particular immune disorder involves the NK-1 receptor pathway.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. For example, MPEP 2163 states in part,

> "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

The skilled artisan cannot envision the genus of the encompassed agents that interfere with function or production of the NK-1 receptor, regardless of the complexity or simplicity of the method of isolation. The skilled artisan cannot envision the full

genus pathological conditions that can be treated by the instantly claimed method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Claims 1-21, 34-42, 44-56, 69-90, 105, 106 and 109-125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of pain or inflammation characterized by involvement with the NK-1 receptor by intravenous or intrathecal administration of the antisense oligonucleotide designated as SEQ ID NO: 11, does not reasonably provide enablement for prevention of such conditions or for other routes of administration of such oligonucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The claims are directed to methods of treating pathological conditions characterized by involvement of the NK-1 receptor using compounds such as oligonucleotides that interfere with the function or production of NK-1 receptor. In

specific embodiments the oligonucleotides include antisense or sense oligonucleotides or ribozymes. Claims 34 and 69 are each directed to methods of treating, attenuating or preventing pain or an inflammatory condition by administration of compounds that interfere with the function or production of NK-1 receptors. Claims 35-42, 44-56 and 70-90 depend from one of these claims and thus include prevention of pain or inflammation. To prevent a pathological condition means to keep this condition from occurring. Using inflammation as an example, to prevent an inflammatory condition means to keep it from occurring in a subject now or in the future.

Although the prior art implicates the NK-1 receptor in inflammatory conditions, the prior art does not teach the particular events that cause the process of inflammation. Based on this lack of knowledge and a reasonable interpretation of prevention, one of skill in the art would conclude that no method known currently will prevent from happening in a subject, now or at any future time, an inflammatory condition that involves the NK-1 receptor pathway.

The specification describes the use of an antisense oligonucleotide to the NK-1 receptor that is designated as SEQ ID NO: 11 and is administered to rats to reduce pain from exposure to a painful mechanical or chemical stimulus. The specification describes examples of intrathecal and intravenous administration of antisense oligonucleotides but does not exemplify other routes of administration. The specification does not provide any specific guidance of how to use compounds that interfere with the function or production of the NK-1 receptor to prevent any disease.

Because no specific method of preventing inflammation is disclosed in the specification, the skilled artisan would have to perform a large and undue quantity of

trial and error experimentation in order to determine how to prevent any disorder related to the NK-1 receptor using compounds that interfere with the function or production of the NK-1 receptor. In addition, to practice the instant invention, the skilled artisan would be required to monitor any subject for the remainder of their lifetime to ensure that the modulator of the invention indeed prevented inflammation from happening in said subject. In this case, the quantity of trial and error experimentation required to determine that a method would actually prevent inflammation and the lack of guidance in the specification regarding the direction in which the experimentation should proceed demonstrate that the instant invention is not enabled.

Claims 18, 45, 79 and 116 depend from claim 1, 34, 69 and 105, respectively, and recite numerous routes of administration for delivery of an oligonucleotide or other compound that interferes with function or production of the NK-1 receptor. At the time of filing of the instant application it was recognized in the art that delivery of oligonucleotides through various routes of administration was unpredictable, for example, oral administration of oligonucleotides was a large obstacle, see for example Agrawal et al. (Pharmacol. Ther. 1997), who teach on page 159 that phosphorothioate oligonucleotides are not orally bioavailable and that other oligonucleotides have very low oral bioavailability. The instant specification discloses intrathecal and intravenous administration of antisense oligonucleotides to reduce pain in rats that have been exposed to a painful chemical or mechanical stimulus but does not provide working examples of any other route of administration. The specification does not describe how to formulate nucleic acid therapeutics to overcome the art recognized inability to deliver

any type of nucleic acid by routes such as oral administration that are considered by the skilled artisan to be unpredictable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 34, 52-56, 69, 86-90, 105, 110, 115 and 123-125 are rejected under 35 U.S.C. 102(b) as being anticipated by Snider et al. (Science 1991).

The claimed invention is directed to methods of treating pain, inflammation or pathological conditions characterized by involvement of the NK-1 receptor by administering to a mammal a compound that interferes with the function or production of NK-1 receptors. In some embodiments the compound is administered intravenously.

Snider et al. disclose CP-96,345, an antagonist of the NK1 receptor. The *in vivo* pharmacological activity of this antagonist was tested by intravenous administration in rats and found to reduce response to substance P (see pages 436, last paragraph). Although Snider et al. are silent with regard to use of this antagonist in treating pain, inflammation or other pathological conditions, the disclosed method shares the step of

the instantly claimed methods and would be expected to have the claimed effects, absent evidence to the contrary.

Thus, Snider et al. disclose all limitations of and anticipate claims 34, 52-56, 69, 86-90, 105, 110, 115 and 123-125.

Claims 1-3, 5-7, 9, 10, 14-21, 34-37, 39, 40, 42, 44, 45, 49-56, 69-72, 74, 75, 77-79, 83-90, 105, 106, 109-111, 113-116 and 120-125 are rejected under 35 U.S.C. 102(e) as being anticipated by Monia et al. (US 6,013,788).

Monia et al. disclose antisense oligonucleotides targeted to SMAD3 that include an oligonucleotide, designated as SEQ ID NO: 17, that hybridizes to nucleotides 1118-1133 of SEQ ID NO: 6 of the instant application. Monia et al. further disclose that the antisense oligonucleotides of the invention can be administered to animals, including humans, in order to treat disease conditions. Monia et al. disclose that routes of administration of the oligonucleotides of the invention include intravenous, intrathecal, and parenteral and dosages range from .1μg to 100g per kilogram. Although the oligonucleotide of Monia et al. is not disclosed as interfering with the function or production of NK-1 receptors, the oligonucleotide is the complement of nucleotides within SEQ ID NO: 6 of the instant application and would therefore be expected to have this function, absent evidence to the contrary.

Thus, Monia et al. disclose all limitations of and anticipate claims 1-3, 5-7, 9, 10, 14-21, 34-37, 39, 40, 42, 44, 45, 49-56, 69-72, 74, 75, 77-79, 83-90, 105, 106, 109-111, 113-116 and 120-125.

Allowable Subject Matter

SEQ ID NO: 41 is free of the art searched.

Pertinent prior art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hua et al. (Journal of Neurochemistry 1998). Hua et al. disclose the administration of antisense oligonucleotides to rats for the purpose of reducing pain. This reference is not considered to anticipate or render obvious the instant invention because Hua et al. demonstrated that their oligonucleotides were effective in reducing pain only when coadministered with the NK-1 receptor agonist substance P.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
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TV
June 19, 2006

TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER